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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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Signed Stephen Hordley

Dated 12 May 2004

Patents Form 1/77

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1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1. Your reference — 101111-1 GB

2. Patent application number *(The Patent Office will fill in this part)* — 0314134.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* — 7822448003

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

THERAPEUTIC AGENTS

5. Name of your agent *(if you have one)* — Thomas Kerr MILLER

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* — AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4TG

Patents ADP number *(if you know it)* — 7822471002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	9
Claim *(s)*	2
Abstract	1
Drawing *(s)*	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 7/06/03

12. Name and daytime telephone number of person to contact in the United Kingdom: Jennifer Bennett - 01625 230148

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

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d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

Therapeutic Agents

Field of the invention

The present invention relates to processes for preparing certain (2*S*)-3-(4-{2-[amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid derivatives.

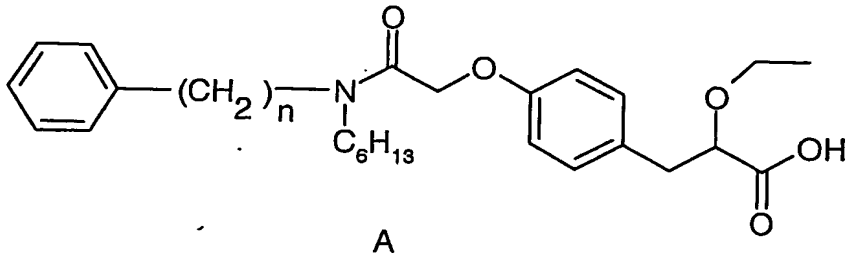
Background of the invention

The metabolic syndrome including type 2 diabetes mellitus, refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinaemia, possibly type 2 diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidaemia observed as deranged lipoprotein levels typically characterised by elevated VLDL (very low density lipoproteins), small dense LDL particles and reduced HDL (high density lipoprotein) concentrations and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In type 2 diabetes mellitus atherosclerosis related conditions cause up to 80% of all deaths.

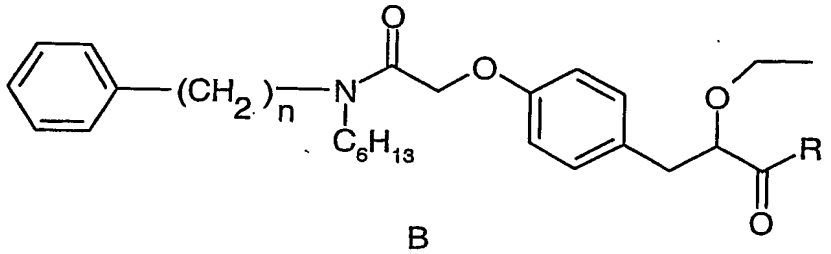
In clinical medicine there is awareness of the need to increase the insulin sensitivity in patients with the metabolic syndrome and thus to correct the dyslipidaemia which is considered to cause the accelerated progress of atherosclerosis. However, currently this is not a universally accepted diagnosis with well-defined pharmacotherapeutic indications.

Co-pending PCT application No. PCT/GB02/05743 discloses compounds of formula A



A

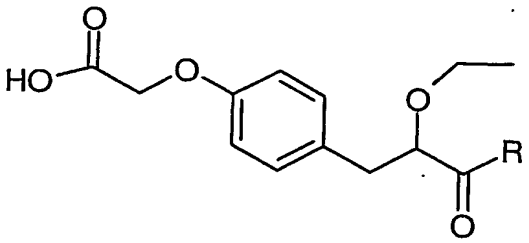
wherein n is 1 or 2 and pharmaceutically acceptable salts, solvates, crystalline forms and prodrugs thereof are highly potent PPARα modulators. A process for the preparation of such compounds is described which comprises reacting the S-enantiomer of a compound of formula B



B

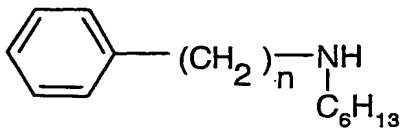
in which n is as previously defined and R represents a protecting group for a carboxylic hydroxy group as described in the standard text "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts, with a de-protecting agent.

Compounds of formula B may be prepared by reacting the S-enantiomer of a compound of formula C



C

in which R is as previously defined with a compound of formula D



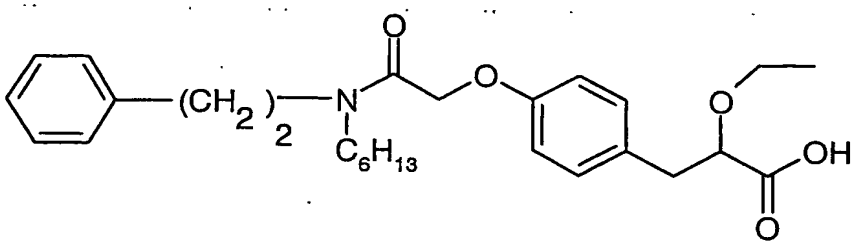
D

in which n is as previously defined in an inert solvent, for example dichloromethane, in the presence of a coupling agent, for example a carbodimide, eg 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide , and optionally in the presence of a catalyst, for example a basic catalyst, eg 4-dimethylaminopyridine, at a temperature in the range of -25°C to 150°C.

An improved process for the preparation of compounds of formula A has now been found.

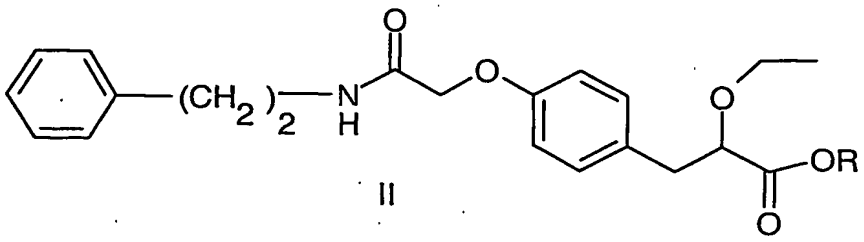
Description of the invention

The present invention provides a process for the preparation of a compound of formula I



I

in which a compound of formula II



II

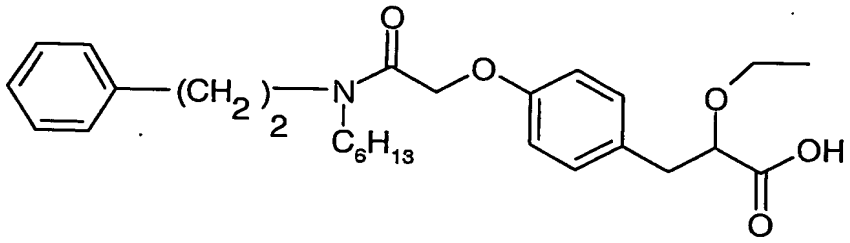
in which R is H or OR represents a protecting group for a carboxylic hydroxy group is reacted with a compound of formula III

$C_6H_{13}X$

III

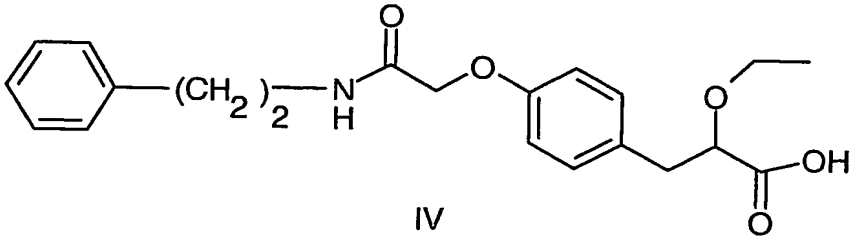
wherein X is a leaving group, in the presence of a base in the presence of an inert solvent at a temperature in the range -25°C to 150°C and optionally, when OR represents a protecting group, removal of the protecting group.

One particular embodiment of the invention provides a process for the preparation of a compound of formula I



I

comprising reacting a compound of formula IV



IV

with a compound of formula III

$C_6H_{13}X$

III

wherein X is a leaving group in the presence of a base in the presence of an inert solvent at a temperature in the range -25°C to 150°C.

The protecting groups OR and deprotecting agents are described in the standard text "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts, which is herein incorporated by reference. Suitable protecting groups include where OR represents a C_{1-6}alkoxy group eg ethoxy group or an arylalkoxy group eg benzyloxy. In particular, when OR represents a C_{1-6}alkoxy group eg ethoxy group or an arylalkoxy group eg benzyloxy, such that COOR represents an ester then such esters may be reacted with a de-protecting agent e.g. a hydrolysing agent, for example lithium hydroxide in a mixture of THF and water, at a temperature in the range of 0-100°C.

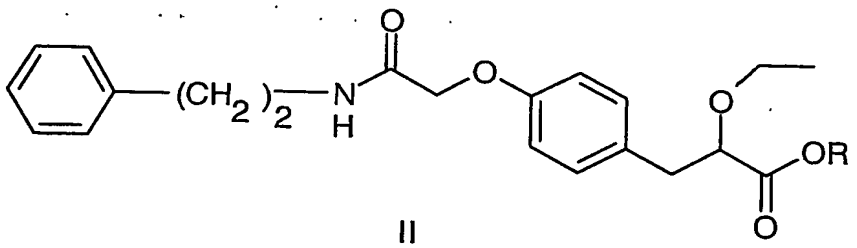
Suitable bases include potassium hydroxide, sodium hydroxide, lithium hydroxide, sodium hydride, potassium *tert*-butoxide, cesium carbonate, potassium carbonate, or sodium carbonate particularly potassium hydroxide.

Suitable inert solvents include dimethyl sulphoxide, *N,N*-dimethylformamide, *N*-methylpyrrolidone or toluene or mixtures thereof, particularly dimethyl sulphoxide.

Suitably X represents bromo, chloro, OSO_2CH_3, OTosyl, OSO_2CF_3, OC(O)OR, $OP(O)(OR)_2$ or OSO_2OR. Particularly X is chloro or bromo.

Optionally a phase transfer catalyst may be used for example an alkylammonium salt for example a tetraalkylammonium halide salt eg tetrabutyl ammonium bromide.

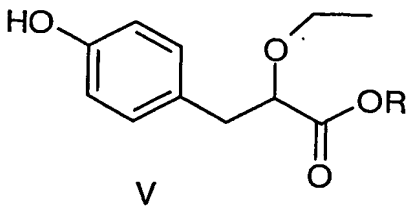
Compounds of formula II in which R is H (or compound IV) may be prepared by reacting a compound of formula II



II

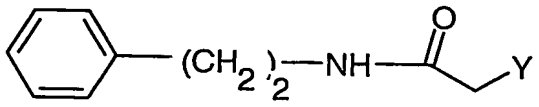
in which OR represents a protecting group for a carboxylic hydroxy group with a de-protecting agent. In particular, OR represents a C_{1-6}alkoxy group eg ethoxy group or an arylalkoxy group eg benzyloxy, such that COOR represents an ester. Such esters can be reacted with a de-protecting agent e.g. a hydrolysing agent, for example lithium hydroxide in a mixture of THF and water, at a temperature in the range of 0-100°C.

Compounds of formula II in which OR represents a protecting group for a carboxylic hydroxy group may be prepared by reacting a compound of formula V



V

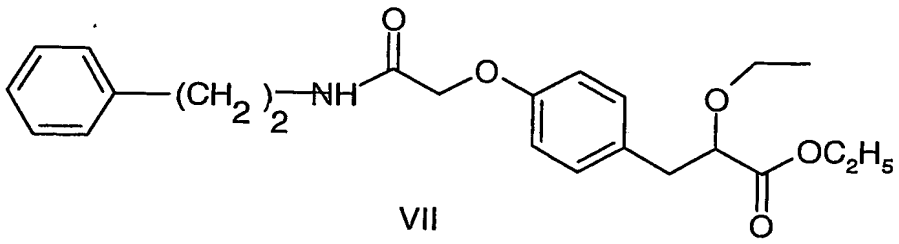
in which OR is as previously defined with a compound of formula VI



VI

in which Y represents a leaving group, for example halo, particularly chloro, in an inert solvent, for example acetonitrile or methyl isobutylketone, in the presence of a base, for example potassium carbonate, at a temperature in the range of 0°C to 150°C.

It is believed that the compound of formula II in which R is H, namely (2*S*)-2-ethoxy-3-(4-{2-oxo-2-[(2-phenylethyl)amino]ethoxy}phenyl)propanoic acid (compound IV) , is novel and is herein claimed as a further part of the present invention. This compound has the advantage of being a solid and therefore offers an opportunity for purification and isolation during the reaction sequence if desired. Also claimed herein is a compound of formula II in which OR represents a protecting group for a carboxylic hydroxy group in particular OR represents for example a C_{1-6}alkoxy group eg methoxy,ethoxy or propoxy or an arylalkoxy group wherein aryl is phenyl optionally substituted by C_{1-6}alkyl, C_{1-6}alkoxy or halo, eg benzyloxy, for example compound VII



VII

In another aspect the present invention provides a process for preparing a pharmaceutically acceptable salt of the compound of formula I comprising reacting the acid obtained by one of the processes of the present invention with a base, optionally in the presence of a solvent and isolating the salt.

Preferably the compound of formula I prepared by the process is the (2S)-enantiomer. Similarly the preferred compounds of formulae II and VII are the (2S)-enantiomers.

Examples

^{1}H NMR and ^{13}C NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at ^{1}H frequencies of 300, 400, 500 and 600 MHz, respectively, and at ^{13}C frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale (δ).

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

Abbreviations

DMSO	dimethyl sulfoxide
THF	tetrahydrofuran
Pd/C	palladium on charcoal
DMAP	dimethylaminopyridine
t	triplet
s	singlet
d	doublet
q	quartet
m	multiplet,
bs	broad singlet
dm	doublet of multiplet
bt	broad triplet
dd	doublet of doublet

Example 1

(2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

a) Phenethylamine (50.10g) was treated with sodium hydroxide (53g) in toluene (260.1g) and water (75ml). A solution of chloroacetyl chloride (56.50g) in toluene (78g) was added under temperature control. After complete reaction, the reaction slurry was heated until a complete solution is obtained, and the water-phase was removed. The organic phase was washed once with aqueous hydrogen chloride and once with water. The resulting toluene phase was reduced by evaporation and diisopropylether was added to the toluene solution.

The solution was cooled and 1-chloro N-phenethylacetamide (71.0 g) was collected by filtration, washed and dried.

b) A mixture of potassium carbonate (122.36g), 1-chloro *N*-phenethylacetamide (52.0g), ethyl (2*S*)-2-ethoxy-3-(4-hydroxyphenyl)propanoate (60.27g) (see WO 99/62871) and acetonitrile (314g) was stirred and brought to the boil under reflux. After complete reaction, the mixture wass cooled and the inorganic salts were filtered off and washed with acetonitrile. The remaining solution was reduced by distillation and diisopropyl ether added. The solution is cooled and ethyl (2*S*)-2-ethoxy-3-(4-{2-oxo-2-[(2-phenylethyl)amino]ethoxy}phenyl)propanoate (82g) is collected by filtration, washed and dried.

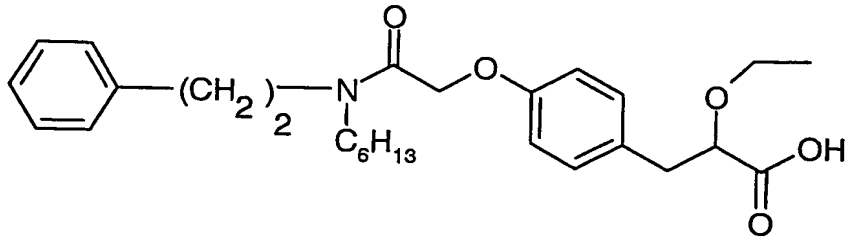
c) A solution of ethyl (2*S*)-2-ethoxy-3-(4-{2-oxo-2-[(2-phenylethyl)amino]ethoxy}-phenyl)propanoate(82.0g) in THF (356g) was added to a solution of lithium hydroxide (14.6g) dissolved in water (600ml) . The mixture was stirred at room temperature. After complete reaction, the mixture was evaporated under reduced pressure to remove THF. After evaporation, the reaction mixture was cooled to room temperature and acidified with hydrochloric acid. The acidified product was extracted with ethyl acetate. The ethyl acetate solution was washed with water and evaporated to a reduced volume. When no more water came off, the residual ethyl acetate solution was diluted with diisopropyl ether to initiate precipitation. (2*S*)-2-Ethoxy-3-(4-{2-oxo-2-[(2-phenylethyl)amino]ethoxy}phenyl)-propanoic acid was filtered off and washed with diisopropyl ether and dried under vacuum.

d) Dimethylsulfoxide (DMSO) (2750 mL), potassium hydroxide powder (244 g) and (2*S*)-2-ethoxy-3-(4-{2-oxo-2-[(2-phenylethyl)amino]ethoxy}phenyl)propanoic acid (250 g) were stirred at approximately 18°C for ca 20 minutes. 1-Bromohexane (344 g = 292 mL) was added over 2.5 hours. The reaction mixture was stirred for approximately 10 minutes. Diisopropyl ether (1000 mL) was added followed by filtration, extraction and separation of the mixture. The DMSO layer was further extracted with diisopropyl ether (2x1000 mL). The DMSO layer was acidified with 4M HCl(aq) (950 mL). Diisopropyl ether (3000 mL) and water (2500 mL) were added followed by extraction. The layers were separated (pH~2 of aq layer) and the diisopropyl ether layer was washed with water (2500 mL). The diisopropyl

ether layer was concentrated *in vacuo* to a clear, very viscous oil. Yield 317 g, assay 88.1%, corrected yield 91.1%, LC-purity 97.2%, e.e. 97.8%.

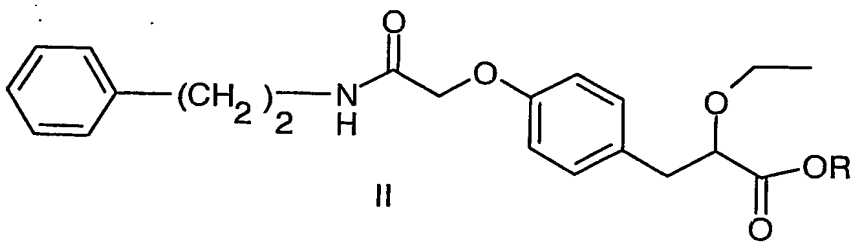
Claims:

1. A process for the preparation of a compound of formula I



I

in which a compound of formula II



II

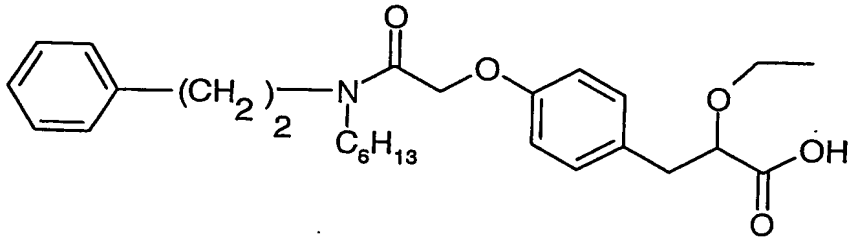
in which R is H or OR represents a protecting group for a carboxylic hydroxy group is reacted with a compound of formula III

$C_6H_{13}X$

III

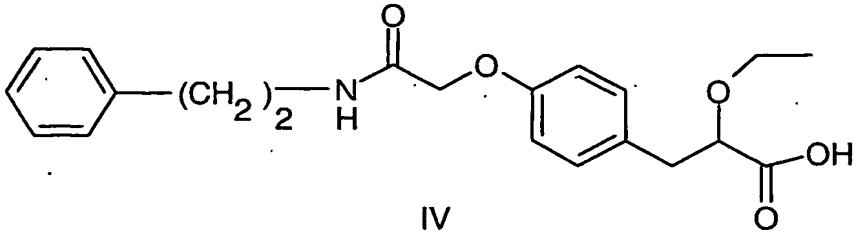
wherein X is a leaving group, in the presence of a base in the presence of an inert solvent at a temperature in the range -25°C to 150°C and optionally, when OR represents a protecting group, removal of the protecting group.

2. A process for the preparation of a compound of formula I



I

comprising reacting a compound of formula IV



IV

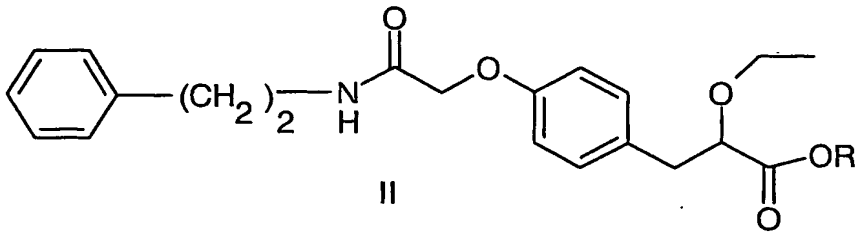
with a compound of formula III

$C_6H_{13}X$

III

wherein X is a leaving group in the presence of a base in the presence of an inert solvent at a temperature in the range -25°C to 150°C.

3. A compound of formula II



II

in which OR represents a protecting group for a carboxylic hydroxy group.

4. A compound according to claim 3 in which OR represents a C_{1-6}alkoxy group.

5. A compound according to either claim 3 or 4 which is the 2S enantiomer.

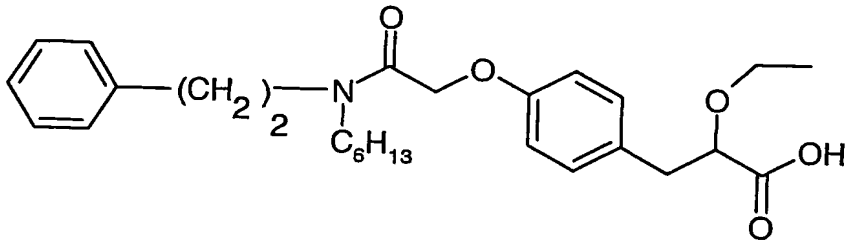
6. The compound (*2S*)-2-ethoxy-3-(4-{2-oxo-2-[(2-phenylethyl)amino]ethoxy}phenyl)-propanoic acid.

7. A process according to claim 1 to produce the (2S) enantiomer of the compound of formula I by using the 2S enantiomer of the compound of formula II.

ABSTRACT

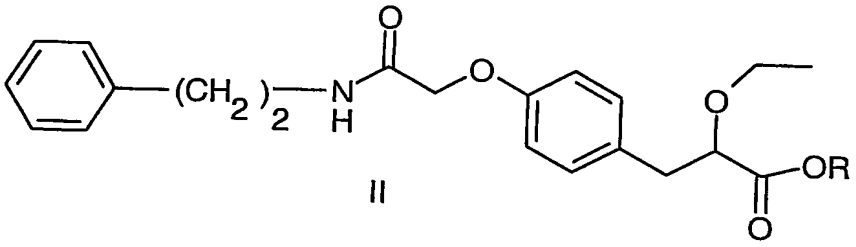
Title : Therapeutic Agents

The present invention provides a process for the preparation of a compound of formula I



I

in which a compound of formula II



II

in which R is H or OR represents a protecting group for a carboxylic hydroxy group is reacted with a compound of formula III

$C_6H_{13}X$

III

wherein X is a leaving group, in the presence of a base in the presence of an inert solvent at a temperature in the range -25°C to 150°C and optionally, when OR represents a protecting group, removal of the protecting group.